EMERGING TREATMENT OF DIABETIC NEPHROPATHY

By

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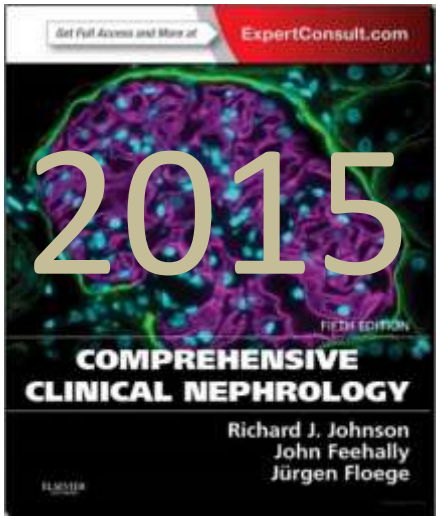
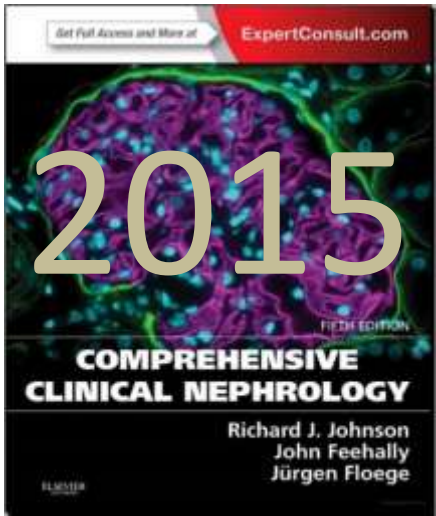
Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in most Western societies. It can develop in the course of 20-40% of all forms of diabetes mellitus.

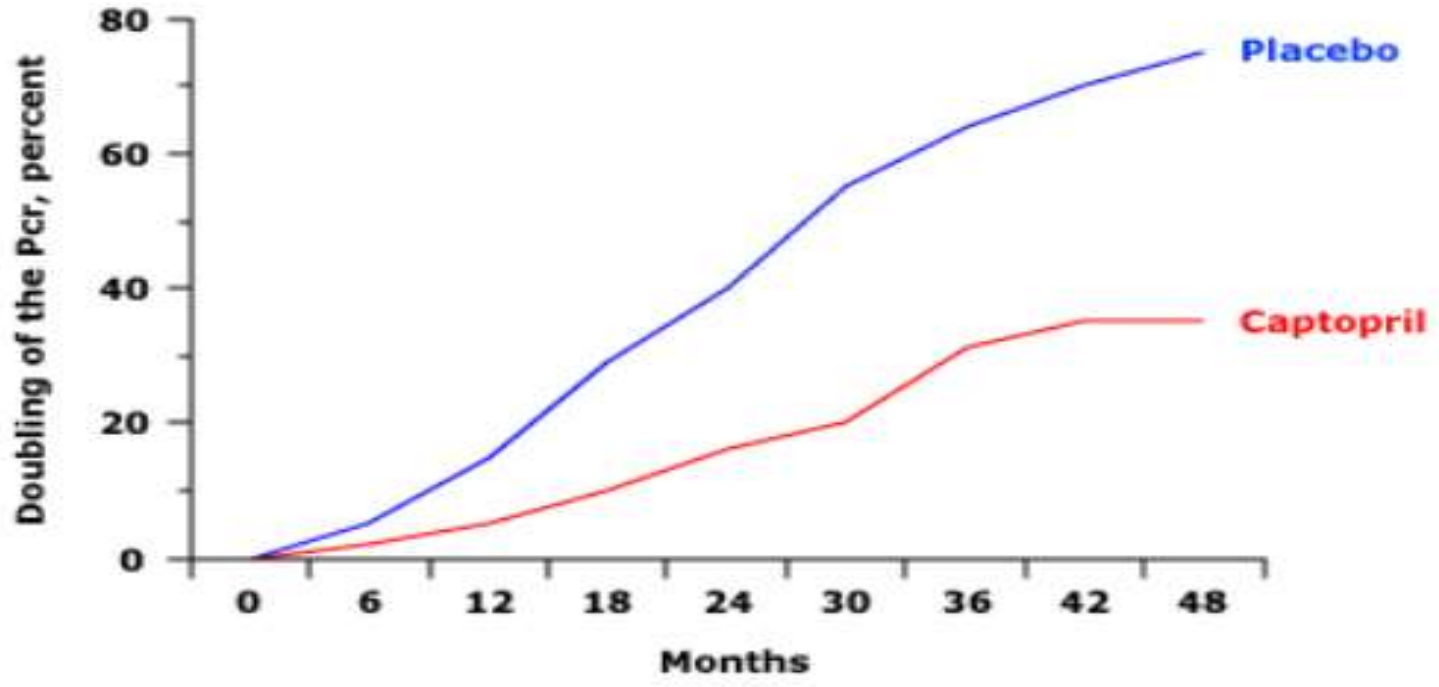


At present the most effective therapeutics for the treatment of DN target the renin-angiotensin system.

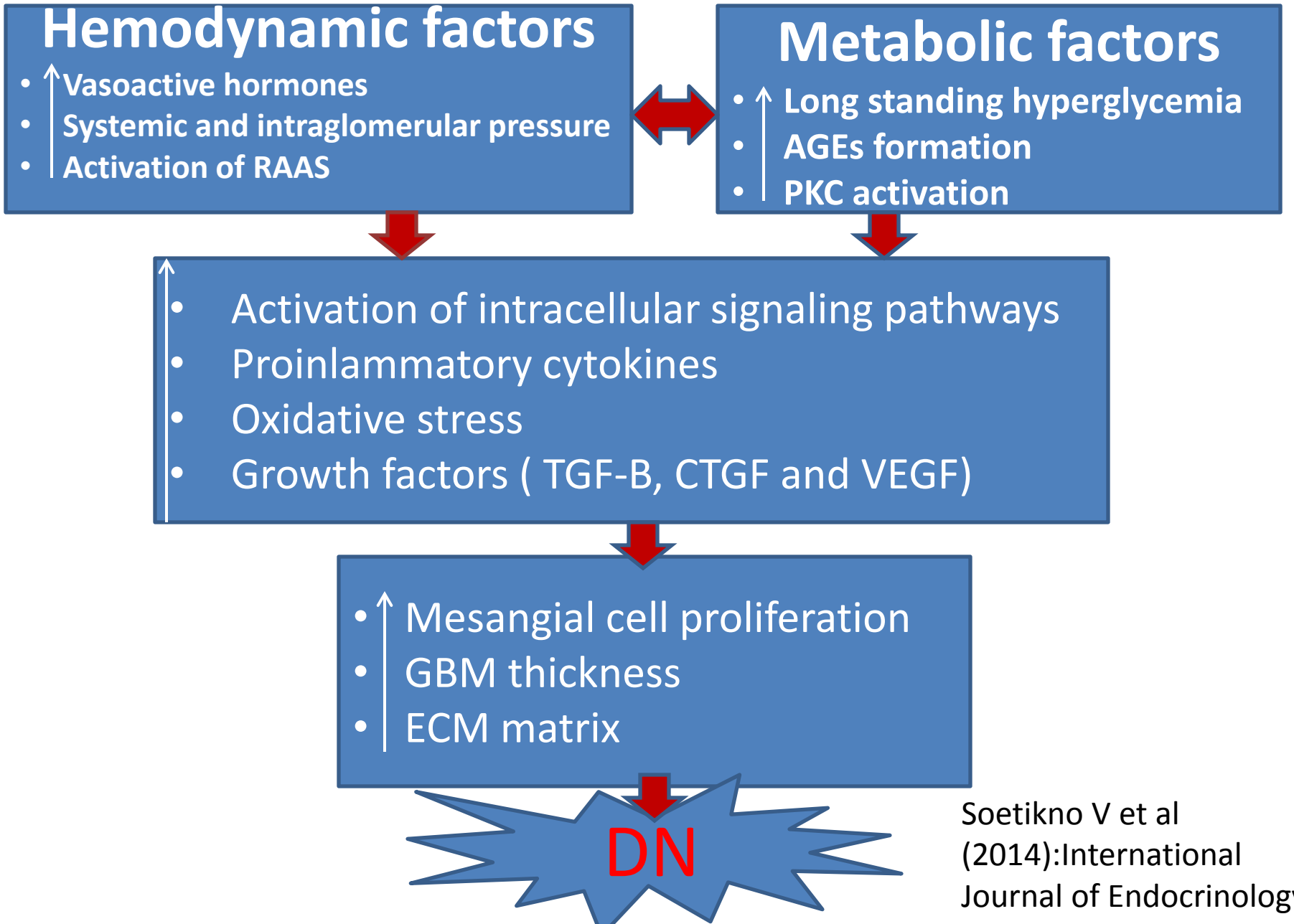


Unfortunately, whilst they slow down the progression of DN they do not prevent it and thus novel therapeutics are required.

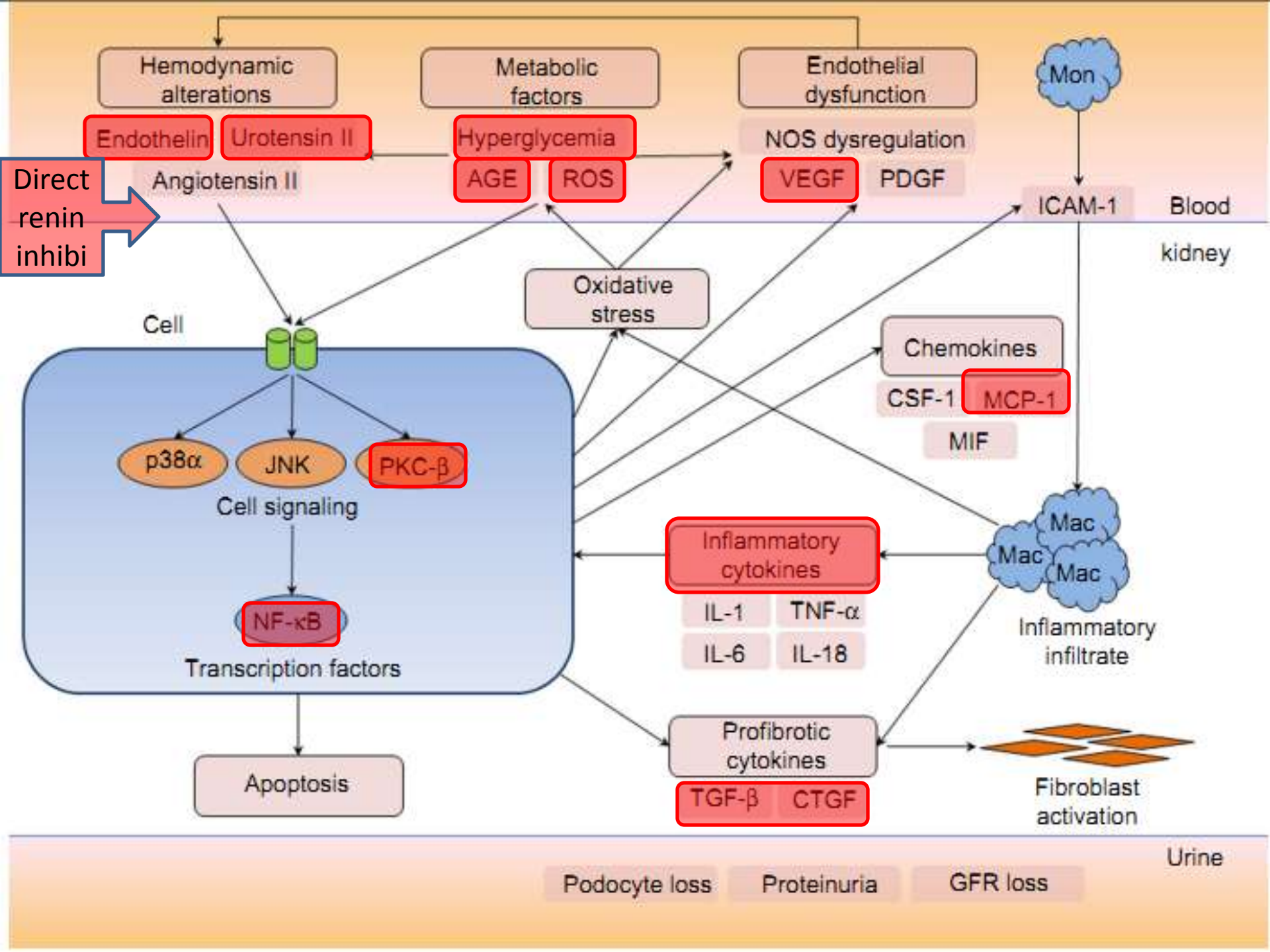
ACE inhibitor slows progression of diabetic nephropathy



Pathophysiology of DN



Soetikno V et al (2014):International Journal of Endocrinology


Hemodynamic alterations
Metabolic factors
Endothelial dysfunction
Mon
Endothelin
Urotensin II
Angiotensin II
Hyperglycemia
AGE
ROS
NOS dysregulation
VEGF
PDGF
ICAM-1
Blood
kidney
Direct renin inhibi
Oxidative stress
Cell
Chemokines
CSF-1
MCP-1
MIF
p38α
JNK
PKC-β
Cell signaling
NF-κB
Transcription factors
Inflammatory cytokines
IL-1
TNF-α
IL-6
IL-18
Mac
Mac
Mac
Inflammatory infiltrate
Profibrotic cytokines
TGF-β
CTGF
Fibroblast activation
Apoptosis
Urine
Podocyte loss
Proteinuria
GFR loss

Clinical Trials run to treat DN

TARGET	PERCENTAGE
Glycaemic Control (including insulin and glucose transport)	→ 14.5%
Advanced Glycation End-Products	1.5%
Reactive Oxygen Species	→ 9%
Inflammation	5%
Renin-aldosterone-angiotensin system	→ 35%
Endothelin	2.5%
Dietary Interventions	→ 17.5%
Pro-fibrotic molecules	2%
Anti-Thrombotic	1.5%
Genetics	1%
Protein Kinase C- inhibitors	1%
Anti-Lipidaemic	4.5%
Calcium Blockers	1.5%
Others – diuretics, hormones, apoptosis,	5%

Renin inhibitors

Aliskiren reduced albuminuria and was more effective than perindopril in reducing interstitial fibrosis in diabetic rats.

AVOID trial

The NEW ENGLAND JOURNAL of MEDICINE

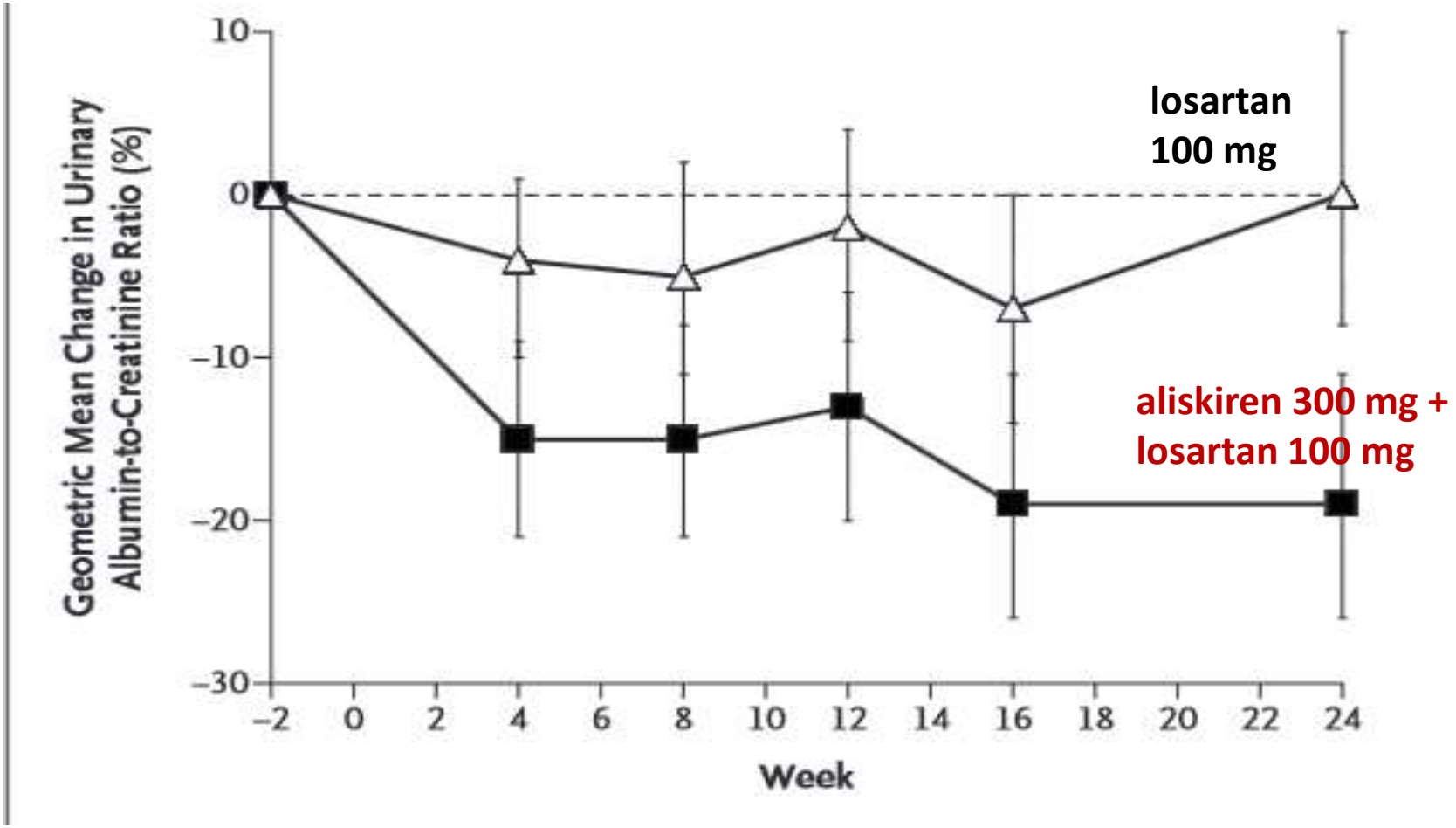
ORIGINAL ARTICLE

Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D., and Norman K. Hollenberg, M.D., Ph.D. for the AVOID Study Investigators

N Engl J Med 2008; 358:2433-2446 | June 5, 2008 | DOI: 10.1056/NEJMoa0708379

AVOID trial (n= 599)



ALTITUDE trial (n=8,561)

ALTITUDE trial (n=8,561) type 2 diabetics.

- Aliskiren 300 mg or placebo plus RAS inhibitors
- No significant difference in renal outcomes.
- The trial was terminated prematurely due to excess hyperkalemia and hypotension in the aliskiren group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans-Henrik Parving, M.D., D.M.Sc., Barry M. Brenner, M.D., Ph.D., John J.V. McMurray, M.D., Dick de Zeeuw, M.D., Ph.D., Steven M. Haffner, M.D., Scott D. Solomon, M.D., Nish Chaturvedi, M.D., Frederik Persson, M.D., Akshay S. Desai, M.D., M.P.H., Maria Nicolaides, M.D., Alexia Richard, M.Sc., Zhihua Xiang, Ph.D., Patrick Brunel, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the ALTITUDE Investigators*

Aliskiren + RAS inhibitors should be contraindicated in patients with diabetes.

The Endothelin inhibitors

- ET-1, ET-2 and ET-3 These vasoactive proteins bind to their receptors ETA, ETB, and ETC.
- ETA receptors have been shown to induce vasoconstriction.
- ET-1 has been found to be elevated and altered expression of the receptors has also been reported in diabetic patients.

Endothelin inhibitors

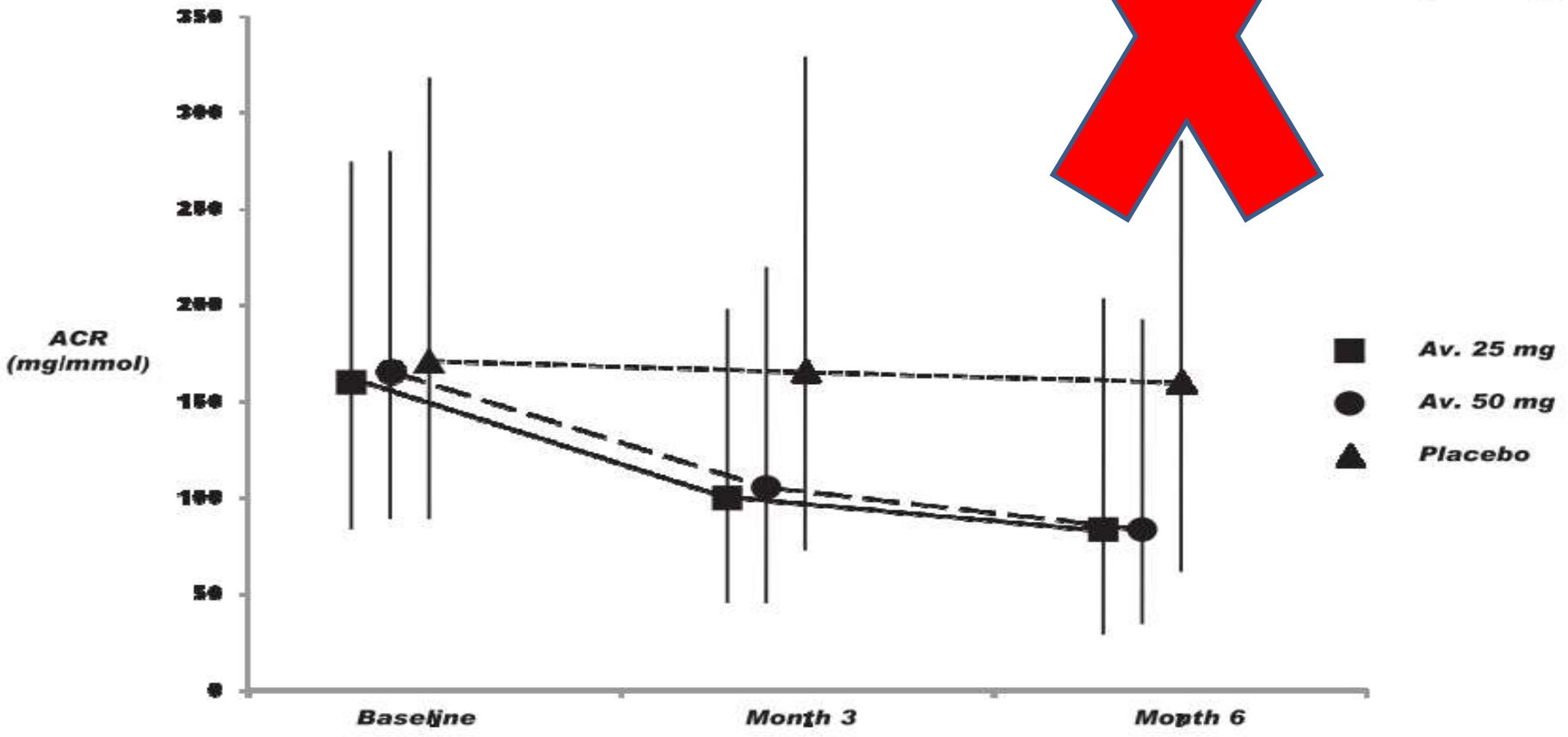
Bosentan
Atrasentan
Avosentan

Renoprotective, reduce albuminuria and reduce renal extracellular matrix (ECM) accumulation diabetic rats.

ASCEND trial (n=1,392)

Avosentan for Overt Diabetic Nephropathy

Johannes F.E. Mann,* Damian Green,† Kenneth Jamerson,‡ [illegible],§
Susan J. Kuranoff,‖ Thomas Littke,‖ and Giancarlo Viberti,¶ for [illegible]ND Study Group



J Am Soc Nephrol 21: 527–535, 2010. doi: 10.1681/ASN.2009060593

In a randomized trial of 211 type 2 diabetics.

- ***Atrasentan*** added to RAS inhibition for 3 months reduced albuminuria.
- Although fluid overload was manageable, but this force more patients to discontinue treatment on the higher dose of atrasentan.

Lim A (2014) :Diabetic nephropathy complications and treatment. International Journal of Nephrology and Renovascular Disease .

The ***SONAR*** trial (NCT01858532): study the effect of *atrasentan on* renal outcomes in type 2 diabetics.

Urotensin R blocker

Urotensin-II (U-II) is the most potent vasoconstrictor peptide ever described.

Palosuran is a competitive antagonist of the urotensin II receptor.

Closel et al, American society for pharmacology and experimental therapeutics 2004 :311,204-212

Clin Pharmacol Ther. 2006 Sep;80(3):246-56.

Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients.

Sidharta PN[1], Wagner FD, Bohnemeier H, Jungnik A, Halabi A, Krähenbühl S, Chadha-Boreham H, Dingemanse J.

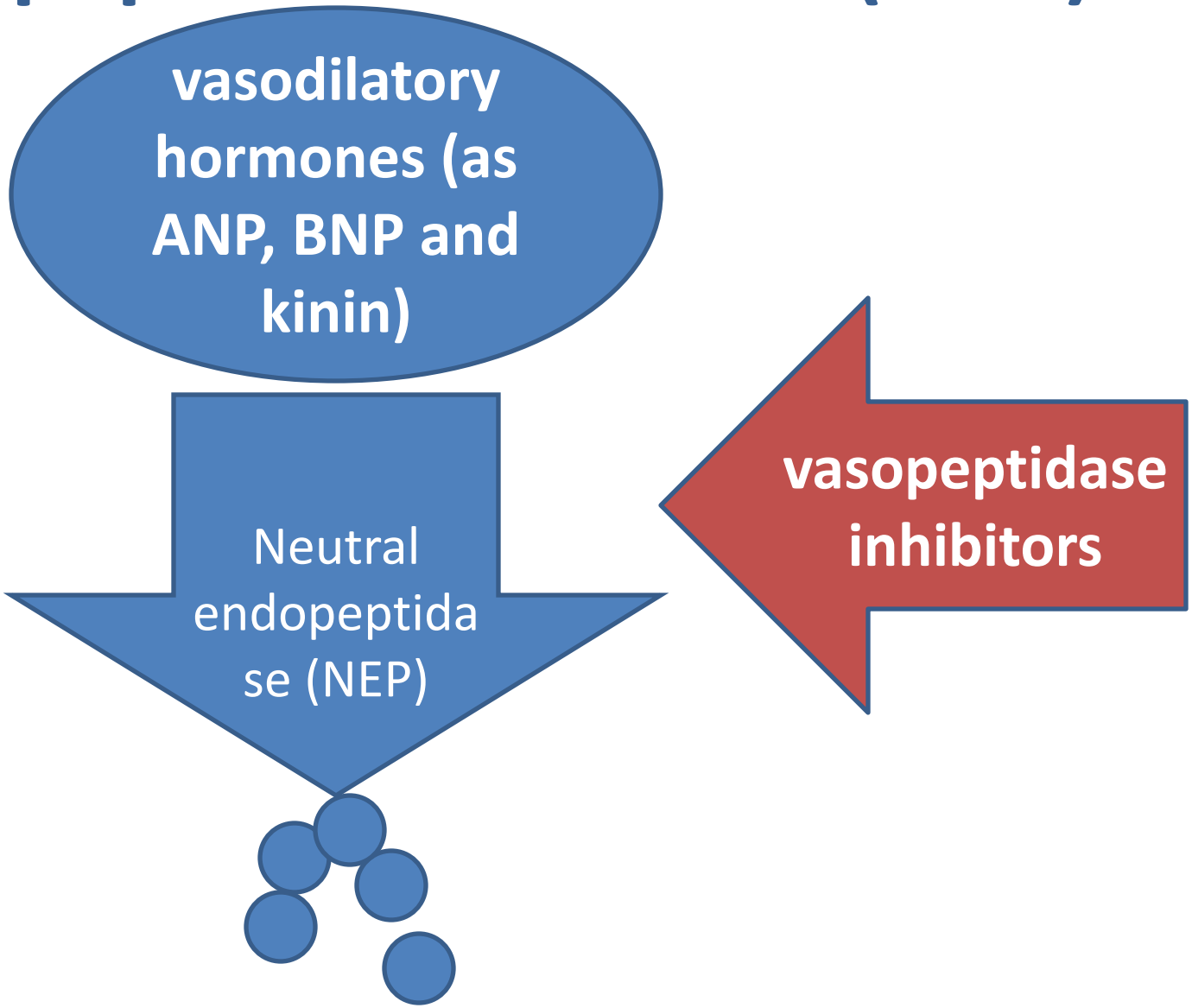
Palosuran plus RAS inhibitors for 2-weeks in diabetic patients with macroalbuminuria, reduced albuminuria by 24%.

Effect of the Urotensin Receptor Antagonist Palosuran in Hypertensive Patients With Type 2 Diabetic Nephropathy

Liffert Vogt, Carlos Chiurchiu, Harbajan Chadha-Boreham, Parisa Danaietash, Jasper Dingemanse, Samy Hadjadj, Henry Krum, Gerjan Navis, Eric Neuhart, Aneliya I. Parvanova, Piero Ruggenenti, Arend Jan Woittiez, Reuven Zimlichman, Giuseppe Remuzzi, Dick de Zeeuw, for the PROLONG (PROteinuria Lowering with urOteNsin receptor antaGonists) Study Group

The ***PROLONG*** trial is RCT in hypertensive type 2 diabetics found no significant reduction in albuminuria after 4 weeks of treatment.

Vasopeptidase inhibitors(VPIs)

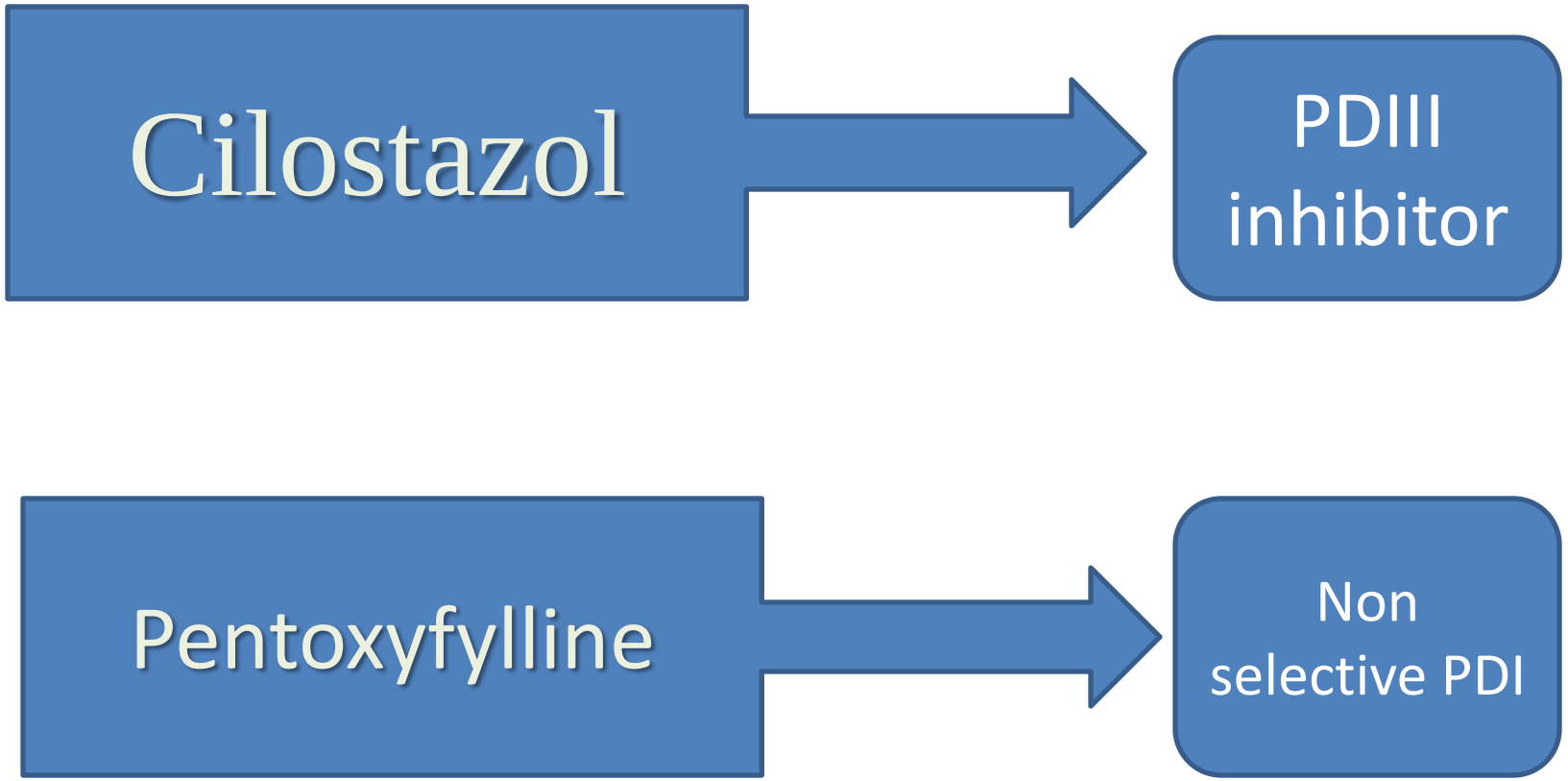


Vasopeptidase inhibitors

Omapatrilat, ilepatril and fasidotril

- Omapatrilat has reno-protective effects in diabetic rats.
- Human data are insufficient.

Phosphodiesterase inhibitors



Pentoxifylline

Pentoxifylline has anti-inflammatory and immunomodulatory properties and lowers blood viscosity.

PTF shows a significant effect in modulating TNF-α, IL-1, and IL-6.

In different models of renal disease where TNF-α plays a central role, such as lupus nephritis and crescentic glomerulonephritis, PTF prevents or attenuates renal injury.

In a meta-analysis of 17 randomized trials involving 991 participants, pentoxifylline was equivalent to captopril in reducing albuminuria and preserving serum creatinine.

However, the studies were small and of poor methodology, with no data on ESRD or mortality.

The Effect of Pentoxifylline on Proteinuria in Diabetic Kidney Disease: A Meta-analysis

Brendan B. McCormick, MD, Amy Sydor, MD, Ayub Akbari, MD, Dean Fergusson, PhD, Steve Doucette, MSc, Greg Knoll, MD, MSc

Received: September 7, 2007; Accepted: January 2, 2008; Published Online: April 23, 2008

Roozbeh et al enrolled 74 patients with type 2 diabetes with overt proteinuria.

- Randomized to pentoxifylline 400 mg daily plus captopril or captopril alone.
- The reduction in proteinuria from baseline was greater in the pentoxifylline-treated group.

Ren Fail. 2010 Jan;32(2):172-8. doi: 10.3109/08860221003602645.

Captopril and combination therapy of captopril and pentoxifylline in reducing proteinuria in diabetic nephropathy.

Roozbeh J[1], Banihashemi MA, Ghezlou M, Afshariani R, Salari S, Moini M, Sagheb MM.

The results of the **PREDIAN** study which study the effect of PTF on DN patients are still expected.

TGF-beta inhibitors

- The key effector in DN.
- TGF-beta has three isoforms.
- Increased expression in DN by hyperglycaemia, AGEs, stretch, AII, endothelin, and oxidative stress.

Administration of (the antifibrotic , anti TGF-beta), **Pirfenidone** at the lower dose of 1200mg (n=77 for 1 yr) resulted in a concurrent improvement in renal function but did not lower albuminuria.

Larger studies are needed to validate the findings.

J Am Soc Nephrol. 2009 Aug;20(8):1765-75. doi: 10.1681/ASN.2008090931. Epub 2009 Jul 2.

Pirfenidone is renoprotective in diabetic kidney disease.

RamachandraRao SP[1], Zhu Y, Ravasi T, McGowan TA, Toh I, Dunn SR, Okada S, Shaw MA, Sharma K.

AGEs

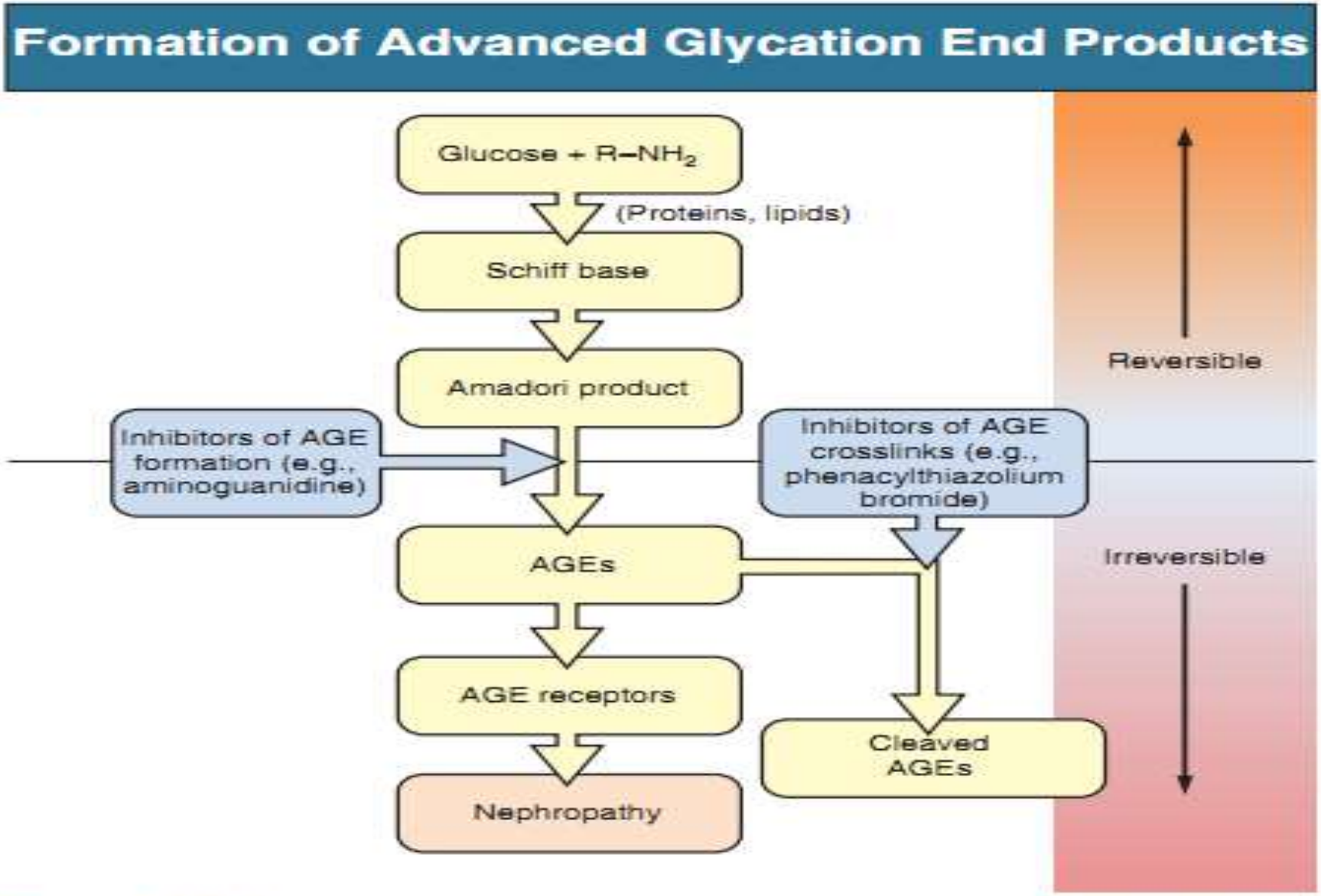
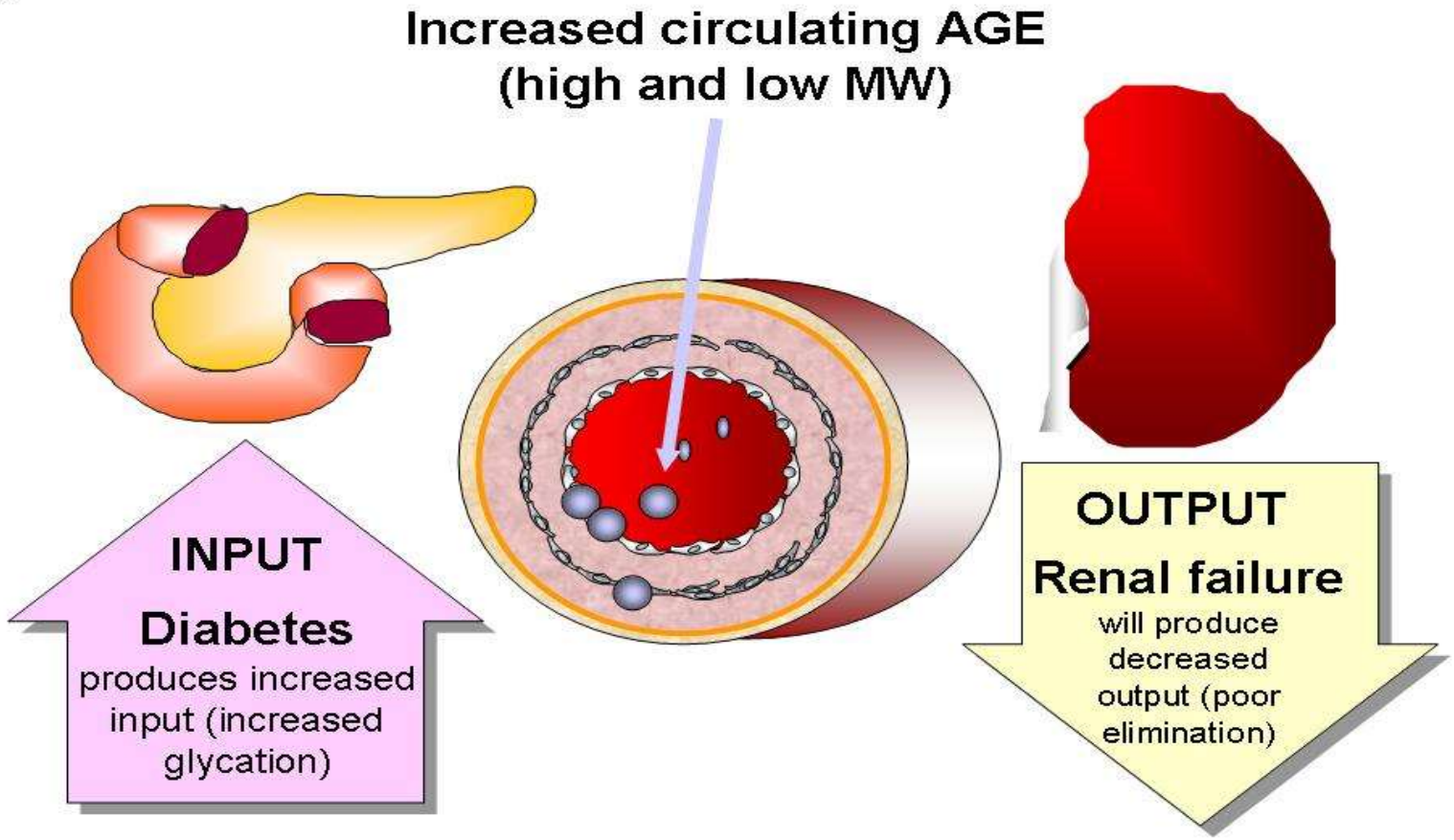
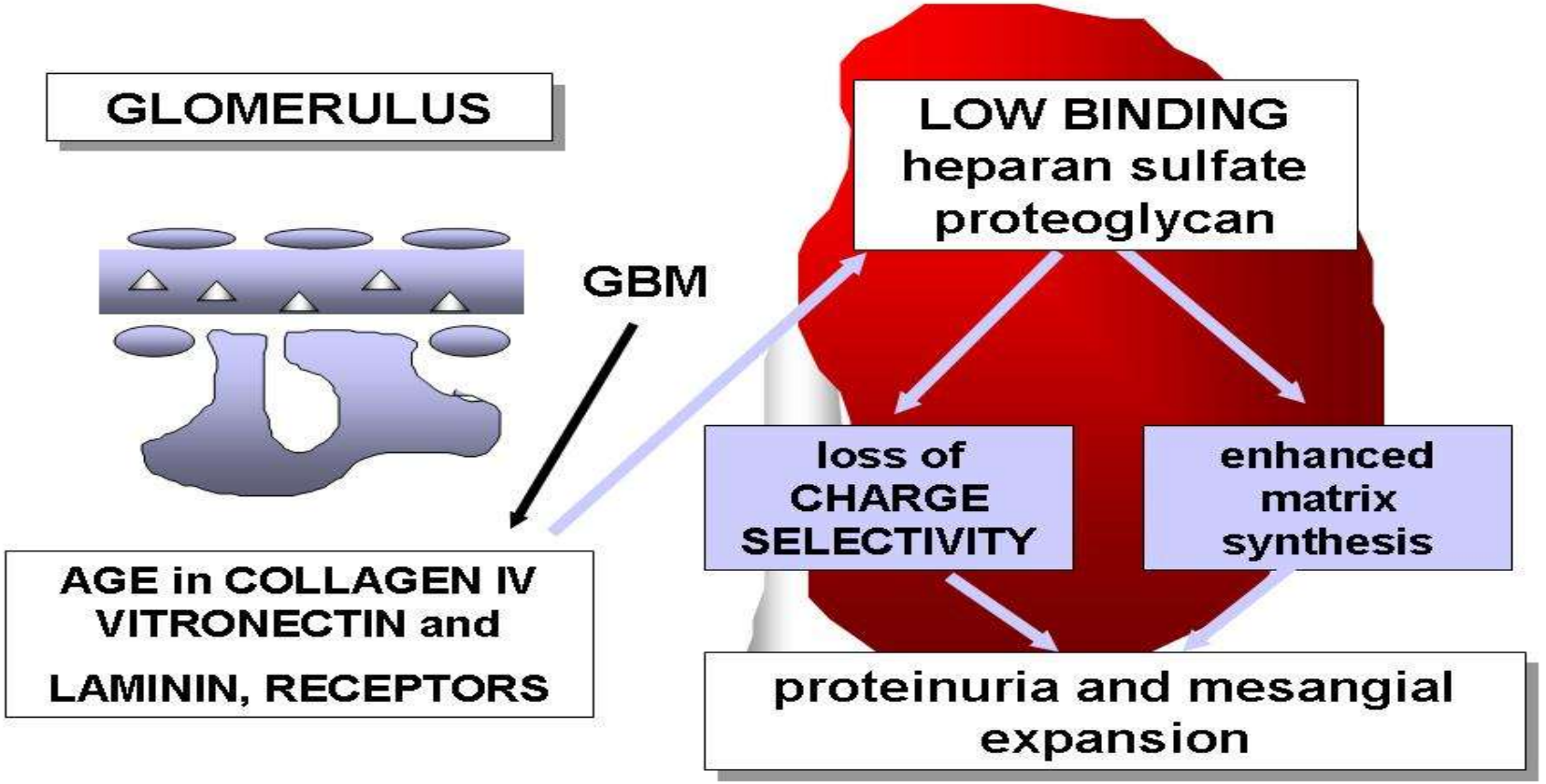


Figure 30-6 Mechanism of formation of advanced glycation end products (AGEs).

Advanced glycation products are metabolized to small peptides



Advanced glycation products in nephropathy



AGES inhibitors

Reduce AGE formation

Aminoguanidine

Pyridoxamine

Benfotiamine

GLY-230

ALT-946

OPB-9195

LR-90

metformin

AGE crosslinks breaker

ALT-711(alegebrium)

Phenacylthiazolium

Aminoguanidine (pimagedine)

Am J Nephrol 2004;24:32–40
(DOI:10.1159/000075627)

Randomized Trial of an Inhibitor of Formation of Advanced Glycation End Products in Diabetic Nephropathy

Bolton W.K. · Cattran D.C. · Williams M.E. · Adler S.G. · Appel G.B. · Cartwright K. · Foiles P.G. · Freedman B.I. · Raskin P. · Ratner R.E. · Spinowitz B.S. · Whittier F.C. · Wuerth J.-P. · for the ACTION I Investigator Group (Appendix) F.

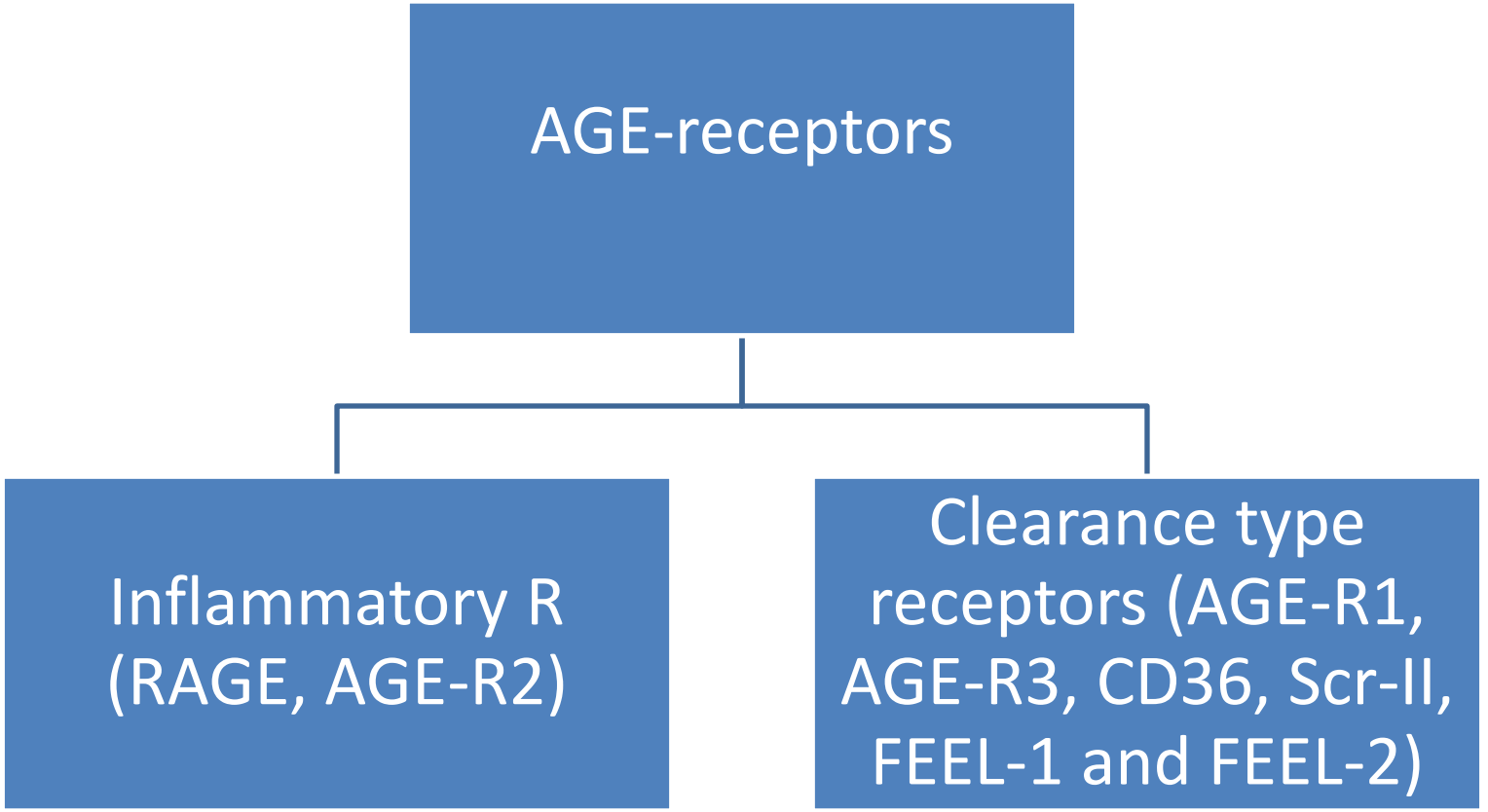
ACTION trial (n=690) type 1 diabetics with overt nephropathy for 2–4 years.

A reduction in proteinuria with Aminoguanidine treatment but no effect on serum creatinine.

Pyridoxamine (intermediate of vitamin B6) inhibits AGE formation and scavenges ROS attenuated the progression of human DN.

- Six months study, pyridoxamine reduced the change from baseline creatinine in type 1 and type 2 diabetics without affecting albuminuria.
- However, in a randomized controlled trial of 317 type 2 diabetics, pyridoxamine treatment for 13 months did not significantly affect serum creatinine.

ALT-711 (alegebrium) is an AGE crosslink breaker, reduced albumin excretion rate, blood pressure and glomerulosclerosis in diabetic rats.



(Vlassara and Bucala 1996; Vlassara 1997; Singh, Barden et al. 2001; Forbes, Yee et al. 2004; Schrijvers, De Vriese et al. 2004; Alikhani, Alikhani et al. 2005).

sRAGEs

One of the actions of RAGE is activation of nuclear factor-κB (NF-κB).

The soluble extracellular domain of RAGE (sRAGE), can act as a decoy receptor and experimentally reduce the renal lesions in diabetes.

Agents targeting oxidative stress

- Bardoxolone methyl
- Vitamin B6 derivatives
- metformin,
- OPB-9195,
- ACEi, AT1 antagonists,
- RAGE

- **Bardoxolone methyl** is a potent activator of Keap1-Nrf2 pathway, which leads to inhibition of the proinflammatory NFkB pathway .

In the **BEAM trial** (n=227) patients with type 2 diabetes and eGFR (20-45 mL/min per 1.73 m2).

- Assigned to either placebo or one of three doses of bardoxolone methyl (25, 75, or 150 mg/day) for 13 months of follow-up.
- Bardoxolone methyl therapy at all three doses significantly increased eGFR by 10 mL/min per 1.73 m2, while placebo therapy had no effect.

However, enthusiasm for bardoxolone methyl therapy is tempered by the following findings:

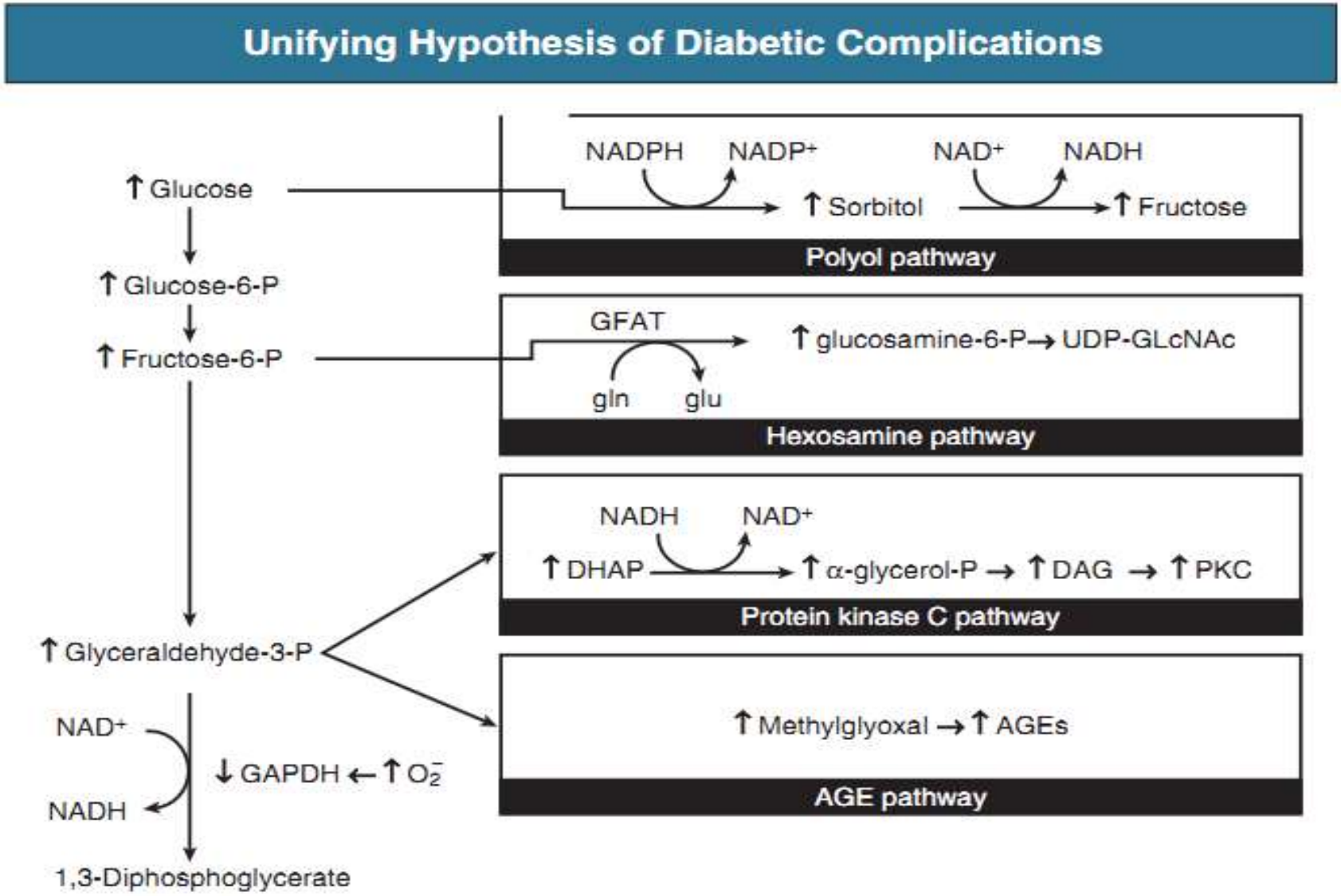
- Increase in intraglomerular hydrostatic pressure. and significantly increased albuminuria.
- The eGFR decreased almost to baseline within 4weeks of stopping therapy.
- Dose-dependent adverse events (muscle spasms and nausea).

In the much larger ***BEACON*** trial (n=2,185) type 2 diabetics with stage 4 CKD

- Bardoxolone 20 mg daily or placebo.
- The trial was stopped after a median follow-up of 9 months due to a higher rate of cardiovascular events and increased albuminuria, with no reduction in ESRD or cardiovascular death.

Further questioning the safety profile in DN.

PKC


Unifying Hypothesis of Diabetic Complications
↑ Glucose
↑ Glucose-6-P
↑ Fructose-6-P
↑ Glyceraldehyde-3-P
NAD+
NADH
↓ GAPDH ← ↑ O2−
1,3-Diphosphoglycerate
NADPH
NADP+
↑ Sorbitol
NAD+
NADH
↑ Fructose
Polyol pathway
GFAT
↑ glucosamine-6-P → UDP-GLcNAc
gln
glu
Hexosamine pathway
NADH
NAD+
↑ DHAP
↑ α-glycerol-P → ↑ DAG → ↑ PKC
Protein kinase C pathway
↑ Methylglyoxal → ↑ AGEs
AGE pathway

PKC has 11 different isoforms.

- ***PKC alpha*** contributes to albuminuria.
- **PKC beta** == mesangial expansion.

Both isoforms may play a role in the generation of reactive oxygen species.

INHIBITORS OF PKC

Ruboxistaurin is a selective inhibitor of PKC-β.

Animal studies with ruboxistaurin showed beneficial effects on reducing mesangial expansion, hyperfiltration, albuminuria, and tubulointerstitial injury.

J Pharmacol Sci. 2006 Aug;101(4):335-43. Epub 2006 Aug 5.

Protein kinase C beta inhibitor LY333531 attenuates intercellular adhesion molecule-1 and monocyte chemotactic protein-1 expression in the kidney in diabetic rats.

Wu Y[1], Wu G, Qi X, Lin H, Qian H, Shen J, Lin S.

Patients with type 2 diabetes (n=132) and early DN on stable doses RAS inhibitors were randomly assigned to receive ruboxistaurin 32 mg/day, or placebo.

- After one year, ruboxistaurin reduce albuminuria and stabilize eGFR independent on BP.
- The effect of ruboxistaurin on long-term (greater than one year) renal, no differences in kidney outcomes were observed between ruboxistaurin and placebo.

-Much larger trials are required before determining the potential clinical role of this agent.

NF-kB

NF-kB activate numerous genes including cytokines, adhesion molecules, angiotensinogen and many other inflammatory and proliferative proteins.

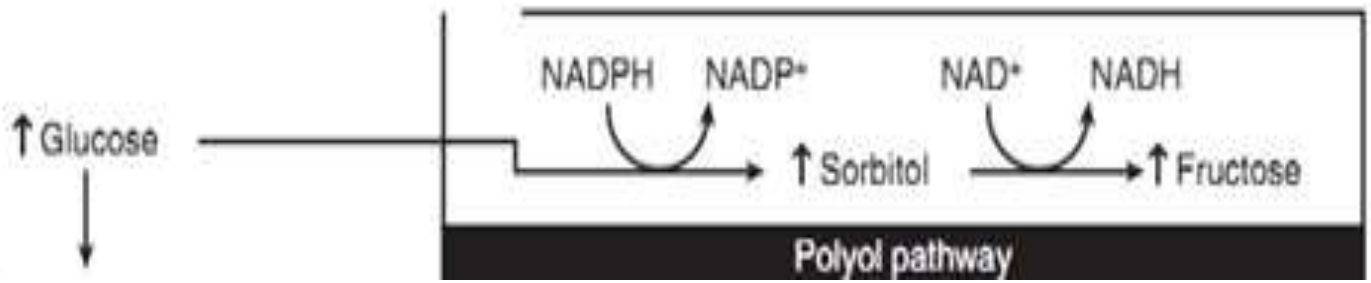
NF-kB is activated by a range of stimuli including glucose, AGEs and ROS.

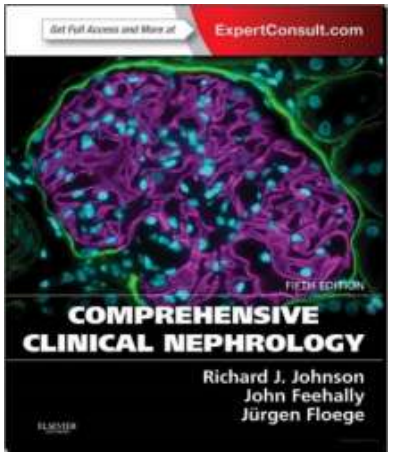
(Barnes and Larin 1997; Bierhaus, Schiekofer et al. 2001).

Pyrrolidine dithiocarbamate (PDTC) is a NF-kB inhibitor is renoprotective, but its toxicity does not allow for direct translation to the clinical setting due to its involvement in a number of essential cellular processes including apoptosis.

Aldose reductase pathway

Leads to depletion of NADPH by aldose reductase leads to inability to regenerate glutathione leading to oxidative stress reactions and cell death.





Aldose reductase inhibitors

J Diabetes Complications. 2001 Sep-Oct;15(5):241-4.

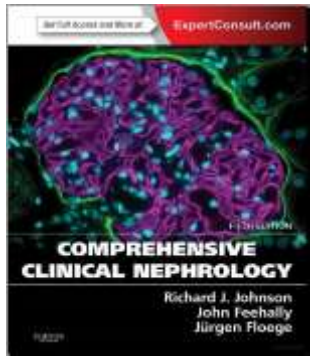
Long-term effect of epalrestat, an aldose reductase inhibitor, on the development of incipient diabetic nephropathy in Type 2 diabetic patients.

Iso K[1], Tada H, Kuboki K, Inokuchi T.

A small study of (35) type 2 diabetics showed that **epalrestat** treatment for 5 years prevented progression of microalbuminuria.

The experience with AR inhibitors in DN has been disappointing, due to hypersensitivity reactions and liver function abnormalities.

More recently, laboratory studies have focused on blocking fructokinase, which is in the distal polyol pathway, with more promising results. However, fructokinase inhibitors have not yet been administered to humans.



Glycosaminoglycans

Sulodexide is a mixture of 80% heparan sulfate and 20% dermatan sulfate.

Sulodexide reduce the enhanced heparan sulfate degradation in the GBM that occurs in DN.

It has anti-inflammatory properties reducing ROS, MCP-1, TGF-β, extracellular matrix expansion, and IL-6 in endothelial cells. It may improve renal hemodynamics.

The **DiNAS** trial (n=223) type 1 and type 2 diabetics with serum creatinine < 1.7 mg/dL.

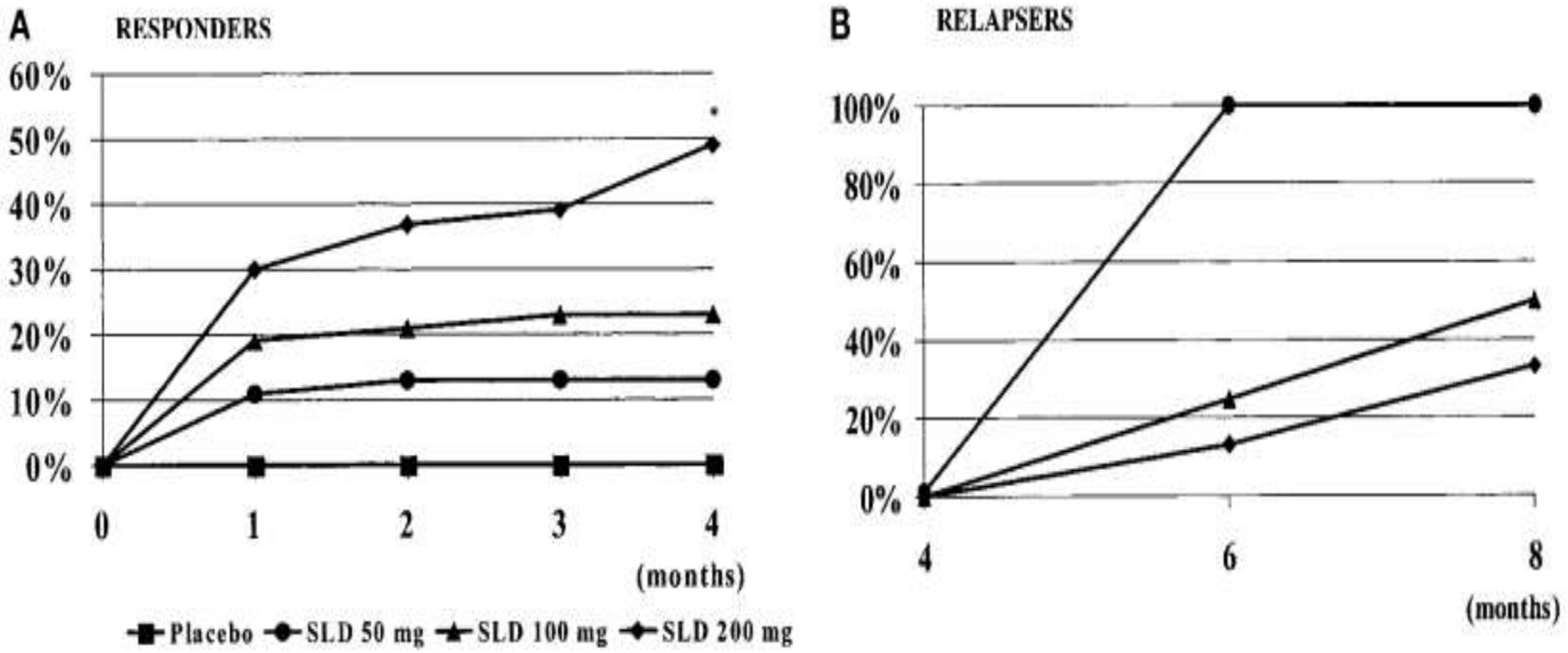
- Sulodexide (50, 100, 200 mg/day) versus placebo for 4 months, with a further 4 months follow-up.
- There was a dose-dependent effect, with 200 mg/day the most effective in reducing albuminuria.

DiNAS trial (n=223)

J Am Soc Nephrol 13: 1615–1625, 2002

Oral Sulodexide Reduces Albuminuria in Microalbuminuric and Macroalbuminuric Type 1 and Type 2 Diabetic Patients: The Di.N.A.S. Randomized Trial

GIOVANNI GAMBARO,* IDA KINALSKA,† ADRIAN OKSA,‡ PETER PONT'UCH,‖ MILUSE HERTLOVÁ,§ JINDRICH OLSOVSKY,¶ JACEK MANITIUS,** DOMENICO FEDELE,†† STANISLAW CZEKALSKI,○ JINDRISKA PERUSICOVÁ,‡‡ JAN SKRHA,‡‡ JAN TATON,§§ WLADYSLAW GRZESZCZAK,¶¶ and GAETANO CREPALDI○



The **Sun-MICRO** trial (n= 1,056) and The **Sun-MACRO** trial (n= 1,248), type 2 diabetics with microalbuminuria on maximum doses of RAS.

- Sulodexide 200 mg/day versus placebo for 12 months. There was no difference between the groups in normalizing albumin excretion or difference in doubling of serum creatinine.
- These studies have dampened the enthusiasm for sulodexide in DN.

Sulodexide for Kidney Protection in Type 2 Diabetes Patients With Microalbuminuria: A Randomized Controlled Trial

Edmund J. Lewis, MD, Julia B. Lewis, MD, Tom Greene, PhD, Lawrence G. Hunsicker, MD, Tomas Berl, MD, Marc A. Pohl, MD, Dick de Zeeuw, MD, PhD, Hiddo Lambers Heerspink, PhD, Richard D. Rohde, BS, Robert C. Atkins, MD, Anne T. Reutens, MD, David K. Packham, MD, Itamar Raz, MD, Collaborative Study Group

Conclusion

Sulodexide failed to decrease urine albumin excretion in patients with type 2 diabetic nephropathy and microalbuminuria.

Stem cell treatment in DN

Chairmen:

*Chairmen Alphabetically Arranged

Prof. Mohamed Ghoneim
Prof. Hussein Sheashaa
Prof. Sayed Hatata
Prof. Yaser Abd Elraoof

Speakers:

12:30 - 12:50	Early diabetic Nephropathy Prof. Magdy Elsaharkawy
12:50 - 01:10	Management of DM in CKD Prof. Wael Farag
01:10 - 01:30	Pancreatic Transplantation in Diabetic Uremic Patients
01.50 - 02.10	Stem Cell Transplantation to Treat Diabetic Nephropathy: Where we Stand?Prof. Mostafa Aniss
02.20 - 02.30	Symposium

Aldosterone antagonism

Thursday 5th , February 2015

First Session 10.00 am – 12.40 pm

Chairmen:

*Chairmen Alphabetically Arranged

Prof. Ehab El Toraby

Prof. Mohamed Ragheb Refaie

Prof. Manal EL Tarshouby

Prof. Nagy Shaaban

Speakers:

10:00 - 10:20	Diabetic Foot in Renal Patients
11:00 - 11:20	Role of Aldosterone in Diabetic Nephropathy Prof. kamal Okasha
[illegible]	Diabetic nephropathy in type 1 DM Prof Ashraf Abdel Basset
11:40-12:00	Primary prevention of diabetic bephropathy Prof. Mohamed Awad
12:00 - 12:20	Discussion
12:20 - 12:30	Symposium
12:30 - 12:40	Coffee Break

vitamin D

Third Session 02.10 pm - 04.00pm

Chairmen:

*Chairmen Alphabetically Arranged

Prof. Ayman Refaei

Prof. Alaa Wafa

Prof. Ghada elkanishy

Prof. Omayma Saleh

Speakers:

02:50 - 03:10 Vitamin D and Diabetic Nephropathy

Dr. Ghada El Said

03:30 - 03:50 Discussion

Lunch

Other emerging treatments

- PPAR-alpha (peroxisome proliferator-activated receptor-alpha) agonist: Fenofibrate Significantly lower the rate of progression from normal albumin excretion to microalbuminuria at 3 years.
- PPAR-gamma agonists: such as the thiazolidinediones reducing fibrosis, mesangial cell proliferation, inflammation and profibrotic cytokines such as hepatocyte growth factor (HGF) and other factors in experimental studies.
- Inhibitors of (SGLT-2) (T-1095): have a renoprotective effect in experimental models of type 1 diabetes.

- MCP-1 receptor antagonist : **propagermanium** in model of diabetic nephropathy, resulted in reduced renal hypertrophy and macrophage infiltration in renal glomeruli.
- Growth hormone and insulin-like growth factors antagonists.
- Selective COX-2 inhibitor.
- Prostacyclin analogue: **beraprost** sodium, reduced albuminuria in type 2 diabetic patients.
- Thromboxane A2 antagonist (S-1452 and OKY-064).

- A humanised anti-CTGF antibody (FG-3019): completed a Phase II study in patients with DN and was well tolerated and improved albuminuria.

- Suppression of VEGF expression with a number of therapies including alagebrium, ACE inhibitors, sRAGE, SU5416 and OPB-9195 remain controversial

- MMF and infliximab.

- microRNA's, histone methylation and metabolic memory.


thank you